131. Meissner's corpuscles / touch-pressure sensation;
132. Merkel's disk / touch-pressure sensation;
133. Pacinian corpuscle / touch-pressure sensation;
134. Ruffini's corpuscle / temperature sensation;
135. retina / visual acuity;
136. parathyroid gland / calcium balance;
137. placenta / placental activity;
138. skeletal muscle fibers / muscle contraction;
139. copora cavernosum / genital vasodilation;
140. corticospinal tract / movement control;
141. motor cerebral cortex / movement control;
142. postganglionic neurons / control of blood pressure and adrenal activity;
143. intramural ganglion / distal colon peristalsis;
144. hypogastric plexus / control of urethral and anal sphincters;
145. pelvic plexus / genital vasodilatation and penile erection;
146. vesical plexus / urinary bladder control; and
147. celiac plexus / intestinal peristolisis.

Claim 76 **(New)** The method of any one of claims 69 or 70 further comprising the step of administering said compound to a mammal and confirming a decrease or increase in said correlated physiological function.

REMARKS

Claims 33, 34, 39, 40, and 45-68 are pending and rejected. Claims **34, 40, 45, 52, 53, 60 and 63-68** have been amended. Claims **33 and 39** have been cancelled without prejudice. New claims **69-76** have been added. Upon entry of this amendment, claims 34, 40, and 45-76 will be pending.

No new matter has been added.

New claims 69-76 have been added. Claims 69 and 70 find support, *inter alia*, in claims 33 and 39, as well as pages 20 (baseline response inhibited by at least 30%), pages

54-63 (reporter systems), and Examples 2-4. Claims 71-74 find support in the claims 41-44 as originally filed. Claims 75 and 76 find support in claims 33 and 39.

Claims 34, 40, 45, 52, 53, 60 and 63-68 have been amended to update dependency and/or to update the step of an independent claim to which they refer.

Election/Traverse

The Office Action states that Applicants cancelled claims directed at non-elected species in the Amendment filed July 19, 2001. Applicants note that such cancellation was premature and accordingly add the subject matter of the cancelled claims as new claims 71-74 which find support in the claims as originally filed.

Applicants note that no prior art has been raised over the subject matter of elected species #116. Accordingly, Applicants respectfully assert that new generic claims 69-70 represent the original scope of the claims as filed. Claims 71-76 read on the elected species.

In accordance with 37 C.F.R. §1.141, Applicants respectfully request the consideration of claims to additional species that include the limitations of the allowed generic claims upon the allowance of one or more generic claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 33, 34, 39, 40, and 45-68 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Applicants respectfully traverse.

The written description requirement of §112, first paragraph, is met so long as the invention is described in the specification as broadly as it is claimed. The written description requirement ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims. *Vas-Cath Inc. v. Mahurkar,* 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

The Office Action alleges that claims 33 and 39 contains an improper Markush group and improperly contained a table. Claims 33 and 39 have been cancelled without prejudice in favor of new claims 69 and 70 which do not contain tables or Markush groups.

The Office Action further alleges that claim 33 was indefinite as "it is not clear

what receptor from which tissue source is correlated with what physiological function." As discussed above, claims 33 and 39 have been cancelled in favor of new claims 69 and 70 further clarify the claimed subject matter.

The Office Action further alleges that the term "abnormal physiological function" renders the claims indefinite because "it is not clear what is an abnormal physiological function so as to allow the metes and bounds to be determined." (Office Action at page 3). Applicants disagree.

It is well established that claims sufficiently define an invention so long as one of ordinary skill can determine what subject matter is or is not within the scope of the claims. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975). One skilled in the art would readily understand the instant usage of the term "abnormal physiological function" as referring to physiological functions linked or associated with diseases or disorders. The art-skilled would readily agree that sweating due to physical exertion or due to high ambient temperatures is ***not*** an "abnormal physiological function". However, abnormal sweating due to a disease or disorder is an "abnormal physiological function". Applicants note that the term "abnormal physiological function" is recited only in dependent claims 67 and 68.

In view of the foregoing, Applicants respectfully request the reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

New Matter

Claims 33 and 39 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing matter that was not described in the specification as filed. Applicants respectfully disagree. The material added to claims 33 and 39 does not constitute new matter because the scope of the amended claim is no broader than (and, thus, is supported by) the specification as filed.

As the Examiner is well aware, it is established law that limitations appearing in claims need not be literally recited in the specification. The issue is not whether words used in the claims are present in the specification but, rather whether the ***concept*** expressed by the words is present. *In re Anderson*, 176 U.S.P.Q. 331 (C.C.P.A. 1973). *See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)* (stating "the description need not be in *ipsis*

verbis [*i.e.*, "in the same words"] to be sufficient").

As set forth in the Lewis declaration (filed with the "Response to Office Action", mailed July 19, 2001), one of skill in the art would understand the correlation between receptor localization and physiological function. These relationships were well known in the art prior to April 14, 1997 (*i.e.,* the priority date for the present application). For example, the Specification states, "Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced." (*See*, page 34, lines 10-12 of the Specification). Therefore, new matter is not believed to be included in any of the amended or new claims based upon, *inter alia,* definitions in the specifications as filed.

Notwithstanding the foregoing, claims 33 and 39 have been cancelled without prejudice. New claims 69 and 70, generally corresponding to cancelled claims 33 and 39, do not contain the material alleged by the Office to be new matter. New dependent claim 75 contains the matter alleged to be "New Matter". As discussed above, Applicants respectfully assert that the material set forth in new claim 75 is not new matter and is supported by the specification.

In view of this fact, reconsideration and withdrawal of the rejection for alleged lack of support respectfully is requested.

Rejections under 35 U.S.C. §§ 101 and 112, first paragraph

Claims 33, 34, 39, 40, and 45-68 were rejected under 35 U.S.C. §101 and 112, first paragraph. As Applicants respectfully assert that the pending claims are in full compliance with the requirements of 35 U.S.C. §§101 and 112, first paragraph, Applicants respectfully traverse this rejection and request its reconsideration and withdrawal.

The Office has acknowledged that "an orphan receptor when directly correlated to a known function, such as affecting food intake or a disease state would have a utility in a method for directly identifying its agonist." (Office Action at page 4). Applicants have previously submitted correlations between the location of a receptor and a physiological activity. Nothing more than routine laboratory experimentation would be required to

determine the localization of a given receptor and thereby the correlated physiological function.

Prior to addressing the points raised by the Office and for purposes of clarity, a brief discussion of 35 U.S.C. §101 and the recently finalized Utility Examination Guidelines is provided.

35 U.S.C. §101 (pre-Utility Examination Guidelines)

To satisfy 35 U.S:C. §101, an invention must be useful. 35 U.S.C. §101 states:

> Whoever invents or discovers any ***new and useful*** process, machine, manufacture, or composition of matter, or any new and useful improvement thereof may obtain a patent therefore, subject to the conditions and requirements of this title. (emphasis added).

In the February 2000 revision of the MPEP, section 2107 states that:

> Deficiencies under the "useful invention" requirement of 35 U.S.C. 101 will arise in one of two forms. The first is where it is not apparent why the invention is "useful." This can occur when an applicant fails to identify any specific utility for the invention or fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The second type of deficiency arises in the rare instance where an assertion of specific and substantial utility for the invention made by an applicant is not credible. (Internal citations omitted).
>
> . . .
>
> Where an applicant has set forth a specific utility, courts have been reluctant to uphold a rejection under 35 U.S.C. § 101 solely on the basis that the applicant's opinion as to the nature of the specific utility was inaccurate.
>
> . . .
>
> The Court of Customs and Patent Appeals has stated that:
>
> > Practical utility is a shorthand way of attributing "real world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate

> benefit to the public.
>
> . . . Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "specific" utility.

The February 2000 revision of the MPEP further cites to a Federal Circuit decision in section 2107 that "[t]o violate [35 U.S.C. §] 101 the claimed device must be totally incapable of achieving a useful result." MPEP 2107, citing *Brooktree Corp. v. Advanced Micro Devices,* Inc., 977 F.2d 1555, 24 USPQ2d 1401, 1412 (Fed. Cir. 1992) (emphasis in MPEP). Additionally, this section of this revision of the MPEP cites *E.I. du Pont De Nemours and Co. v. Berkeley and Co.* (620 F.2d 1247, 1260 n.17 (8th Cir. 1980) for the proposition that "the defense of non-utility cannot be sustained without proof of total incapacity."

Utility Examination Guidelines

The Utility Examination Guidelines state that they were promulgated to assist Office personnel in their review of applications for compliance with the utility requirement under 35 U.S.C. §101. Specifically, the August 2001 revision of the MPEP states that:

> These Guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility requirement. ***The Guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112,*** nor are they designed to obviate the examiner's review of applications for compliance with all other statutory requirements for patentability. The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. MPEP 2107 (emphasis added).

The guidelines were published in the Federal Register on December 21, 1999, and were finalized in the Federal Register on January 5, 2001.

The interim utility guidelines were subsequently revised to include an additional standard to those previously used in a §101 analysis for establishing whether a claimed invention provides proper utility. This new guideline shifted from a standard originally requiring the claims to provide *any* specific utility that is credible to a standard requiring

a specific ***and*** substantial utility that is credible ***or*** which provides a well-established utility. These revisions did away with "throw away" utilities because, according to the Office, such utilities were not specific and substantial. Thus, without a doubt, the revised guidelines *de facto* raise the bar for compliance for utility under 35 U.S.C. §101.

As discussed above, Applicants note that "utility" under 35 U.S.C. §101 is assessed from a "minimal" perspective. Almost *any* evidence of utility (excluding "throw away" utilities) is sufficient under 35 U.S.C. §101.

To summarize, the Utility Examination Guidelines require that a claimed invention provide a specific *and* substantial utility that is credible, or that the claimed invention must provide a well established utility that is immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

Examination of Claims

In evaluating the patentability of an application, the Patent Office has the initial burden of presenting a *prima facie* case and providing evidentiary support of unpatentability. The Court of Appeals for the Federal Circuit stated in *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, (Fed. Cir. 1992), that a "*prima facie* case is a procedural tool of patent examination, allocating the burdens of going forward as between examiner and applicant." *Oetiker* at 1445; *see also* MPEP §2107.01(f)(i) Consideration of a Response to a *Prima Facie* Rejection For Lack of Utility. The Court further stated, "[a]fter evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *Oetiker* at 1445. A "preponderance of the evidence" is a standard of proof by which evidence for one position is of greater weight or more convincing than the evidence which is offered in opposition, and as a whole shows that the fact sought to be proved is more probable than not. Once the Patent Office provides a *prima facie* case, an applicant must provide evidence in response; if, on balance, the applicant's ***evidence*** is not counterbalanced by ***evidence*** presented by the Office, the rejection cannot be sustained. The word "***evidence***" thus becomes key to this analysis: when an applicant provides: facts; data; declarations by experts; third party references; etc. in rebuttal to a rejection, if the Office does not provide equal or greater evidence to rebut applicant's

position, than the applicants have prevailed by a preponderance of evidence and the rejection must be withdrawn.

In a recent article written by Stephen Kunin, the Deputy Assistant Commissioner for Patent Policy and Projects, Deputy Assistant Commissioner Kunin discussed the newly implemented Utility Examination Guidelines. *See*, Kunin, S., 82 J. Pat. & Trademark Off. Soc'y 77 (2000). Applicants draw particular attention to Deputy Assistant Commissioner Kunin's discussion of the new Utility Guidelines and the procedures to be taken by the Patent Office when reviewing patent applicants for compliance with the new "substantial" utility guidelines. Deputy Assistant Commissioner Kunin summarized the steps required to be taken by the Office as follows:

> 1. Read the claims and the written description to ascertain what has been claimed and whether the claims define a statutory subject matter.
>
> 2. Determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible. However, if there is a well-established utility, no rejection under section 101 should be made.
>
> 3. If the Office determines that the claimed invention provides neither a specific, substantial utility that is credible nor a well-established utility, the Office should reject the claimed invention under §101. Further, the Office should reject the claimed invention under §112, first paragraph for failure to disclose how to use the claimed invention.
>
> 4. Once the Office has established prima facie showing of no specific and substantial credible utility, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by providing in the form of a declaration under 37 C.F.R. §1.132 or a printed publication that rebuts the prima facie case by showing that the claimed invention has a specific and substantial utility that is credible or by showing a well-established utility for the claimed invention.

See, 82 JPTOS at 94-95 (2000).

In addition to Deputy Assistant Commissioner Kunin's discussion on proper Office practice in these matters, in his position as Deputy Assistant Commissioner for Patent Policy

and Projects, Deputy Assistant Commissioner Kunin makes clear how the Office must treat statements made by the applicants and/or by third parties in an effort to rebut a *prima facie* case made by the Office. According to Deputy Assistant Commissioner Kunin, the Office ***must*** regard as true any statements of fact made by applicants with respect to an asserted utility; if the Office does not regard the statement as true, the Office must provide ***evidence*** showing that one of ordinary skill in the art would not believe the statements to be true. Further, as Deputy Assistant Commissioner Kunin stated, it would be improper to disregard any opinions made by a qualified expert in the particular field, whose opinion is based upon relevant facts, simply because the Office disagrees with the significance or meaning of the facts provided. (*See*, 82 JPTOS at 95 (2000); *see also* Utility Examination Guidelines, *supra*. Indeed, if the Office rebuts the scientific opinion of a declarant, an applicant can request, and the Office must supply, an Examiner Declaration to support the rebuttal by the Office. (*See*, 37.C.F.R. §1.107 and MPEP §2144.03).

Summary of the Claims

Claims 33, 34, 39, 40, and 45-68 are pending in this application. Claim 33, for example, recites a method for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous G protein coupled receptor (GPCR). The location of expression of the receptor in a mammalian tissue source is known and the receptor has been correlated with at least one mammalian physiological function. No endogenous ligand for the receptor has, as yet been identified. The method comprises the steps of:

(a) subjecting the GPCR to constitutive receptor activation to create a constitutively activated GPCR;

(b) contacting the non-endogenous candidate compound with the constitutively activated GPCR;

(c) identifying the non-endogenous candidate compound as an inverse agonist or an agonist to the constitutively activated GPCR by measuring at least a 30% difference in a reporter signal induced by the contacted compound as compared with a reporter signal in the absence of the contacted compound.

The Claims Satisfy the Requirements of 35 U.S.C. § 101, before and after the Promulgation of the Utility Examination Guidelines

Claims 33, 34, 39, 40, and 45-68 stand rejected under 35 U.S.C §101 because the claimed invention is allegedly not supported by either a specific *and* substantial asserted utility or a well established utility. As will be established below, Applicants' claimed invention provides both a specific *and* substantial utility, and based upon the Specification and with the knowledge of one skilled in the art, a well-established utility.

The Claims Provide a "Specific Utility"

The pending claims provide a specific utility. As acknowledged by the Patent Office, the specification identified several uses including "direct identification of candidate compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents, receptor screening, disease/disorder identification and/or selection, medicinal chemistry and in pharmaceutical compositions."

The Asserted Utility is Credible

According to U.S. Patent and Trademark Office Training Materials For Revised Interim Utility Guidelines ("Guidelines"), Promulgated on March 7, 2000, a well established utility is a "specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." (*See*, page 7 of the Guidelines).

As noted above, specific utilities have been disclosed. Applicants respectfully believe that a credible utility has also been provided, *i.e.*, whether the assertion of utility is "believable to a person of ordinary skill in the art based on the totality of the reasoning provided." (*See*, page 5 of the Guidelines). The claimed invention relates in some embodiments to constitutively activated orphan receptors. Because ligand-dependent activated receptors have been used for discovering modulators of the receptor function, then ligand-independent activated receptors (*i.e.*, constitutively activated receptors) can also be utilized, and have been utilized by Applicants, to discover compounds which act as inverse agonist or agonists of the receptor. Therefore, Applicants' asserted utility cannot be

questioned when all evidence and reasoning provided by the Specification is believable to a person of ordinary skill in the art. *See*, page 5 of the Guidelines.

The Claims Have Substantial Utility

Claims 33, 34, 39, 40, and 45-68 have been rejected under 35 U.S.C. §101 because the claimed invention allegedly is not supported by either a specific ***and*** substantial asserted utility or a well-established utility. According to the Office:

> A '**substantial utility**' is a utility that defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a '**real world**' context of use are not substantial utilities. A '**well established utility**' is a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A 'well established utility' must also be specific and substantial as well as credible."

The Office Action presents two arguments that are said to show that the asserted specific utility is not substantial. As best understood, the Office asserts that:

1) Because an orphan receptor, does not have, by definition, a corresponding endogenous ligand that is known, neither the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on a specific disease state; and

2) Similarly, constitutively activated orphan receptors have no known function.

Based upon these two arguments, the Patent Office alleges that:

> "Since neither the specification nor the art of record disclose any activities or properties that would constitute a 'real world' context of use for the claimed method of identifying compounds having activity of inverse agonist or agonist activity, further experimentation is necessary to attribute a utility to constitutively activated orphan receptors and to the compounds that bind the constitutively activated orphan receptors.
> (Office Action, pages 6-7)

The inaccuracies and deficiencies of the Patents Office's allegations are set forth below.

Response to Office Position 1:

> "Because an orphan receptor, does not have, by definition, a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease state."

An Endogenous Ligand Is Not Required To Understand Receptor Function: Third Party Publications; Declaration of Stanley J. Watson, M.D., Ph.D.

Utilizing commercially available reagents, kits and protocols, an orphan receptor, *e.g.,* the expression of a GPCR (without a known endogenous ligand) of interest to an artisan and selected by the artisan can be determined in specific tissues and regions within the body, including diseased or normal tissue. Upon determining the expression pattern of, *e.g.,* the GPCR, a person of ordinary skill in the art is readily able to ascertain and assess the function of a receptor. Orphan receptors can be prioritized based upon the needs of the artisan desirous of exploiting this information, and one of ordinary skill in the art can utilize Applicant's claimed invention to directly identify candidate compound(s) that act as an inverse agonist or agonist to the receptor. It is well known in the art that the expression pattern of a receptor provides the opportunity for one skilled in the art to develop information relevant to the normal function of the orphan receptor, and also for the opportunity to examine receptor distribution in tissues from disease states to assess clinical relevance. Those skilled in the art have stated that:

> Tissue-specific expression of genes can provide clues to their role in pathology. (Browne, M.J. 78 J. Biotechnology 247, 248 (2000)).

> With the cloning of receptors, pharmaceutical research can follow a conceptual direction which is reverse to the traditional one...[S]ome advanced knowledge of the implications of the receptor-ligand system is desirable, but a significant place has to be left to the serendipitous discovery of therapeutic indications. The serendipity aspect of this endeavor may seem non-economical at first, but is bound to become increasingly accepted. After all, serendipity has been a large part of some resounding pharmaceutical success...[I]f novelty is the driving force in drug research, then entering the drug design at a stage when the biological system is not fully understood is a necessity. The ultimate reward of reverse pharmaceutical research is bound to be, in some cases, the marketing in drugs for large unmet medical needs. Civelli, O. et al 848 Brain Research 63, 64 (1999)

Applicants respectfully direct the Patent Office's attention to the declaration filed in the present application of Stanley J. Watson, M.D., Ph.D. (hereinafter, "Watson Decl."), an additional copy of which is attached hereto as **Exhibit 1**.

Dr. Watson is One of Skill in the Art

Dr. Watson is a Professor & Research Scientist, in the Department of Psychiatry and Mental Health Research Institute, at the University of Michigan. At the University of Michigan, Dr. Watson also serves as the Associate Chair for Research, Department of Psychiatry. In 1970, Dr. Watson received his Ph.D. in Clinical Psychology from the University of Iowa, and in 1974 his M.D. from Tulane Medical School. Dr. Watson is licensed to practice medicine in the states of Louisiana, California, and Michigan. He is Board Certified in Psychiatry and Neurology. In addition, Dr. Watson has been on the Editorial Boards of several journals, including: Neuropsychopharmacology; Critical Reviews in Neurobiology; Molecular Neurobiology; and Peptide Research. Dr. Watson has been invited and has presented at over 100 scientific conferences and is an author and/or co-author of over 300 scientific papers. (*See*, Watson Decla. ¶1).

Dr. Waston declares that he has read the application, the Office Action issued by the Office and data presented herewith and has formed a scientific opinion, based upon his experience and the data provided to him, as to the utility of the claimed invention. Dr. Watson further declares that he is familiar with the technology as set forth in the claims for direct identification of inverse agonists and agonists. (*See,* Watson Decla. ¶4). Based upon the totality of the information and his background, Dr. Watson disagrees with the conclusions reached by the Office that there is not a well-established utility for the claimed invention. (*See,* Watson Decla. ¶5).

Dr. Watson opines that although having knowledge of a receptor's endogenous ligand is useful in defining the receptor function, such knowledge is ***not required*** to understand receptor function. Instead, in Dr. Watson's opinion, where a receptor is expressed, the systems and circuits within which a receptor is expressed in normal versus disease state, and changes in receptor expression in response to certain conditions provide a plethora of information that can readily guide a scientist having routine skill to an understanding of the function of the receptor, without an absolute requirement of knowing the endogenous ligand for the receptor. (*See*, Watson Decla. ¶11). Simply stated, the

function of an orphan can be understood before the endogenous ligand is identified, ***and the tools and skills necessary to secure this information are within the purview of the artisan who has selected an orphan receptor of interest to the artisan.***

Those in the art previously understood that an advantage in identifying the endogenous ligand was to stabilize the receptor in its active state and search for compounds that interfere with the ligand for the binding site (*e.g.*, an antagonist). This simplistic and incorrect thinking prompted scientists to believe that one cannot identify, in the case of GPCRs, GPCR modulators without first having access to the GPCR's endogenous ligand. (*See*, Watson Decla. ¶15). It was not until relatively recently that the scientific community began to appreciate that the conformational states of GPCRs exists in equilibrium between a basal state (generally referred to as "R") and an active state (generally referred to as "R*") where the receptor is able to function, and the receptor shifts from R to R*, and *vice versa*, in equilibrium. (*See*, Watson Decla. ¶17). In Dr. Watson's scientific opinion, the belief that receptor's exists in either an "on" and "off" position, whereby the endogenous ligand is required to turn the receptor "on" (*i.e.*, in the R* state), does not provide an adequate assessment of the GPCR function; rather, the location of a GPCR coupled with the respective cell types, circuits and organs strongly links that GPCR to its physiological function, and with a more modern-based understanding of the equilibrium states of GPCR function, provides a primary tool in understanding receptor function. (*See*, Watson Decla.¶22(a)(1)(a)).

Since the early 1990's, assays have been developed and kits manufactured to aid in the determination of a receptor's function. Such technologies include: homology data between receptors with an unknown and a known function; co-localization analysis with receptors with a known function; dot-blots; *in situ* analysis; northern analysis; and RT-PCR. These techniques have been utilized for over a decade and have become routine practice within the art for determining the distribution of the receptor and assessing their respective function.

Indeed, Applicants are not claiming receptor function. Applicants are not claiming receptors. Applicants are not claiming techniques for defining receptor function or in identifying orphan receptors. These are mere selection-based aspects, the tools for which are well within the scope of the claims. As with any method that may ultimately result in a pharmaceutical, rarely, if ever, is the first compound that is discovered the compound that is

approved by the Food and Drug Administration (FDA). Indeed, it is through the routine and well known process of medicinal chemistry that selected criteria, *e.g.,* potency, stability, *etc.*, are established. But, this being said, the compound that has defined attributes, *e.g.,* an inverse agonist to a selected orphan receptor, is a ***valuable*** material that itself has real world uses. Thus, by focusing on the ***function*** of orphan receptor, the Office creates a "straw-person" argument. This is not appropriate. The claimed method must be reviewed based upon what is claimed -- and since, as is established herein, understanding orphan receptor function is ***independent*** of the claimed method and a matter of the selection by an artisan, the following merely provides a brief overview of how readily the skilled artisan can ascertain the function of a selected orphan receptor.

Techniques Used to Ascertain Receptor Function

The traditional approach to determining receptor function relies upon finding the endogenous ligand prior to searching for receptor modulators (generally antagonists). In stark contrast, the claimed invention relies on a constitutively activated orphan receptor to directly identify candidate compounds (inverse agonists or agonists) without the need for the receptor's endogenous ligand.

According to Dr. Watson, inverse agonists and agonists are classes of compounds that, by definition, must affect the function of the receptor, *e.g.,* the receptor's signaling consequences and response to activation and/or inhibition of function. (*See,* Watson Decla. ¶22(a)(1)(a)). These compounds, by definition, do not simply bind to a receptor but also must affect the function of the receptor.

Indeed, based upon the ***evidence*** provided herein, the Office is incorrect in stating that because an orphan receptor, by definition, does not have an endogenous ligand that is known, that the function of an orphan receptor cannot be determined. As Dr. Watson makes clear in his declaration, in his opinion the function of orphan receptors can be ascertained and assessed using routine procedures within the purview of a person of ordinary skill in the art, *e.g.,* through homology data, or traditional tissue distribution methods, for example, Reverse Transcription-PCR ("RT-PCR"), dot-blots, northern-blots, co-localization analysis and *in situ* hybridization. Determining the tissue distribution of a receptor can be accomplished by purchasing commercially available kits and following manufacturer's instructions. Table A below lists several examples of

routine techniques and commercially available kits, used to determine the tissue distribution of a receptor and the manufacturer of the kit, reagents and protocols utilized to accomplish these routine techniques.

TABLE A

Technique	Manufacturer/Protocol
RT-PCR	Clontech
Dot-Blot	Clontech
Northern Analysis ▪ RNA isolation from cells ▪ Synthesis of probe ▪ Hybridization	 ▪ Gibco/BRL ▪ Stratagene ▪ Clontech
In situ Hybridization ▪ rTth DNA Polymerase ▪ Autoradiography ▪ Male Sprague-Dawley Rats	 ▪ Perkin Elmer ▪ Kodak XAR-5 film ▪ Charles River
Co-localization	Protocol set forth in Marks, D.L. et al, 3 *Mol. & Cell. Neuro.* 395 (1992)
Homology Analysis	DNA STAR™

In Dr. Watson's opinion, it is routine for a skilled artisan to determine the location of a receptor within the body. (*See,* Watson Decla. ¶22(a)(1)(a)). Not only does Dr. Watson assert that determining the location of a receptor helps in the understanding receptor function, but others knowledgeable in the field of functional genomics have agreed with this position: "the expression pattern can determine whether a receptor is expressed in a normal or diseased tissue of interest as a therapeutic target," and that a "highly selective tissue expression profile can also provide a clue to receptor function." (*See*, Browne, M.J, 78 *Biotechnology* 247, 248 (2000)).

As is apparent, those in the art of drug discovery understand that ascertaining the function of a receptor simply requires the use of routine skill and technique together with commercially available products. The knowledge of the endogenous ligand alone is neither dispositive nor required.

Applicants also point out that, especially in view of 37 C.F.R. §1.107 and MPEP §2144.03, the Office has not supported its assertions with anything other than the opinion of the Office. *Oetiker* requires withdrawal of the rejection based upon the Watson Declaration.

Application of Commercially Available Techniques with Orphan GPCRs to Deduce Receptor Function

Following routine techniques disclosed in the manufacturer's instructions of commercially available kits, one skilled in the art would readily be able to determine a receptor's tissue distribution, whether the receptor is expressed in diseased or normal tissue cells, if the receptor target is homologous to other known receptors or, based upon the distribution, the functional role of a receptor.

The function of a receptor is not determined, as the Office incorrectly stated, by first identifying the endogenous ligand. In the early development of understanding receptor function, the ligand was thought to be required to identify modulators that act on the receptor of interest. In Dr. Watson's opinion, knowing a priori, the endogenous ligand is not required in understanding the function of an orphan GPCR, because a skill artisan can appreciate a functional role before the endogenous ligand is identified. (*See,* Watson Decla. ¶22(a)(1)(a)). It is again noted: on the basis of Dr. Watson's Declaration alone, in the absence of ***evidence*** proffered by the Office in support of its position, that the rejection under Section 101 must be withdrawn upon reconsideration.

The following are examples of utilizing routine techniques and commercially available reagents, procedures and kits to aid in understanding and determining receptor function. It is noted that none of the following orphan GPCRs are the subject of collaborations between Arena and a third party. Those collaborations involve different GPCRs, the majority of which are orphan GPCRs that were provided to Arena by a third party.

Receptor Function: Regulation of Insulin Secretion

Utilizing routine techniques and commercially available procedures, kits and reagents, an orphan receptor 19AJ was determined to be naturally constitutively active. A whole-cell cAMP assay comparing the endogenous 19AJ with a control (pCMV) was utilized. (*See*, cAMP Assay Protocol, **Appendix B1** and **Appendix B2** for the graphic results). **Appendix B2** evidences that 19AJ produces about a 20 fold increase in cAMP compared to the control.

Again, utilizing a commercially available human tissue dot-blot format (Clontech), the endogenous 19AJ receptor was used to probe for a determination of the areas where 19AJ is localized. (*See*, Dot-Blot Protocol, **Appendix B3**). According to the results, 19AJ is abundantly expressed in the pancreas (D3) and fetal liver (G4). (*See*, **Appendix B4**). On these basis of this information, 19AJ was considered to have a role in pancreatic functions, such as insulin production.

To confirm the results obtained from the RNA dot-blot, a reverse-transciptase PCR technique ("RT-PCR") was utilized. RT-PCR was performed using 19AJ specific primers and human multiple tissue cDNA panels (Clontech) as templates. Taq DNA polyermase (Stratagene) was then utilized for the PCR reaction. (*See*, RT-PCR Protocol, **Appendix B5**). The 16 human tissues in the cDNA panel utilized (brain, colon, hart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus, leukocyte, and liver) evidenced a single 19AJ band only from the pancreas (panel G). (*See*, **Appendix B6**).

With the knowledge that the pancreas plays a major role in the production of insulin, a northern blot analysis was further utilized with RNA from several exocrine and endocrine pancreatic cell lines and determined that 19AJ receptor was expressed in several insulin-derived glucose-responsive cells. (*See*, Northern Analysis Protocol, **Appendix B7** and **Appendix B8** for the results). These data indicate that even without knowing the endogenous ligand to the 19AJ receptor, one of ordinary skill in the art using routine skilled techniques can understand and assess the functional role of 19AJ, *i.e.*, 19AJ is involved in insulin secretion. (*See*, Watson Decla. ¶19).

Based upon the determination that (a) 19AJ is naturally constitutively active, (b) 19AJ is specifically expressed in the pancreas, and more specifically in the beta cells in the islets of the pancreas and (c) the cells expressing 19AJ are insulin producing, glucose-responsive which substantially increased insulin secretion, this orphan receptor was selected for direct identification of candidate compounds that would exploit this information, *i.e.,* an agonist. Accordingly, the claimed invention was applied to 19AJ and this method led to the direct identification of a candidate compound, Cmpd A, according to the protocol disclosed in the Specification. To confirm that Cmpd A functions to stimulate the production of insulin, a routine technique was utilized, together with commercially available procedures, kits and reagents, to determine that Cmpd A

increases the insulin production in the presence of glucose when compared to the basal level of 19AJ. (*See*, Insulin Assay Protocol, **Appendix B9** and **Appendix B10** for the results). Appendix B10 compares glucose-responsive insulin secreting cell line ("Tu6") and Tu6 transfected with 19AJ ("Tu6/19AJ"), both in the presence of Cmpd A. Comparing Tu6/19AJ in the presence and in the absence of Cmpd A, cells transfected with 19AJ in the presence of Cmpd A evidence about a two (2) fold increase in insulin production. (*See also,* Watson Decla. ¶22(a)(2)(a)).

Based upon the foregoing, and in accordance with the claimed invention an agonist of a constitutively activated 19AJ receptor was directly identified even without knowing the endogenous ligand for 19AJ. This small molecule thus provides the basis for development of small molecule therapeutics for the treatment of, *e.g.,* diabetes.

Receptor Function: Regulation of Feeding

The orphan GPCR 18F was determined to evidence natural constitutive activation. Utilizing a reporter assay, a routine technique, together with commercially available procedures, protocols kits and reagents, the relative light units generated upon receptor expression were measured. (*See*, CRE-Luc Reporter Assay Protocol, **Appendix C1** and **Appendix C2** for graphic results). Utilizing *in situ* hybridization, a routine technique, tissue samples were examined for expression of orphan receptor 18F. (*See*, In situ Hybridization Protocol, **Appendix C3**). It was determined that the 18F receptor is expressed in the following areas of the brain: hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex. 18F receptor is presented in the dark areas in **Appendix C4**; **Appendix C5** provides a reference map of the rat brain. Based upon the localization pattern, a relationship between the 18F receptor and metabolism and/or feeding behavior was surmised.

In situ hybridization analysis, according to the protocol of **Appendix C3**, was conducted using routine techniques on both lean and obese male Zucker rats. As those in the art appreciate, Zucker rats are genetically bred to result in animals that exhibited a lean or obese phenotype. **Appendix C5** provides a representative tissue section of 18F receptor expression in the lean Zucker animals; **Appendix C6** provides a representative tissue section of 18F receptor expression in the obese Zucker animals; and **Appendix C7** is a reference map of this section of the rat brain.

Based upon these data, and based upon the opinion of Dr. Watson, the distribution of 18F in the hypothalamus indicates involvement in feeding behavior. Therefore, the function of the 18F receptor in obesity was indicated by these data. (*See also*, Watson Decla. ¶22(a)(2)(b)).

In further evaluating the 18F receptor as a target receptor of interest, the protocol described in Marks, D.L. et al., 3 Mol. & Cell. Neuro. 395 (1992) was utilized to functionally assess the co-localization of 18F with that of the neuropeptide agouti-related peptide (AGRP), which is known to be related to feeding behavior. AGRP was analyzed in conjunction with radiolabeled 18F and both were found to be co-localized in the arcuate (*see* **Appendix C9**). **Appendix C9** provides results from a co-localization experiment, evidencing that 18F and AGRP are co-localized within the arcuate. The arrow directs attention to a specific cell within the arcuate, with the circle surrounding the cell; the "dots" are radiolabeled 18F, and beneath those, in a darker shade, is AGRP. Given the role that AGRP plays with respect to homeostasis, and further given that 18F is constitutively active in its endogenous state, the results obtained would be consistent with these data in that the almost immediate, significant loss of weight can be understood in the context of 18F influencing AGRP.

In determining that the 18F receptor was a receptor target of interest, the claimed invention was applied to directly identify a candidate compound, ARE112[1]. **Appendix C10**, attached hereto, is a primary plate profile evidencing inverse agonist activity of directly identified compound ARE112 to 18F receptor, utilizing the claimed methods. As a candidate lead compound, ARE112 evidenced a decrease in food intake after intracerebroventricular (ICV) and oral (PO) administration. The in vivo protocols are attached hereto as **Appendix C11** and the results are presented in **Appendix C12**[2]. These data indicate that the orphan GPCR 18F is an orphan receptor target for use in the discovery of compounds that could be useful in the treatment of obesity. These data illustrate the utility of the claimed invention in rapidly identifying small molecule regulators of therapeutically-relevant GPCRs.

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[1] ARE112 is a compound directly identified in accordance with the claimed invention; no position is taken as to whether or not this may be the actual compound used for the potential treatment of *e.g.*, obesity.

[2] ARE112 is a compound which is disclosed and claimed in a co-pending and commonly assigned patent document PCT Application Number PCT/US00/04945.

The location of 18F receptor makes available to the skilled artisan the receptor's functional role. Upon utilizing routine techniques, it is possible to understand the internal mechanism of a receptor of interest to directly identify compounds that modulate the receptor that are potentially useful in the treatment of disorders such as obesity. Application of the claimed invention has led to the direct identification of the compound ARE112 that is an inverse agonist of 18F receptor. ARE112 was then administered to animals to determine the in vivo effects of the compound. As is apparent in **Appendix C12**, the treated animals decreased food consumption, increased fat metabolism and lost weight. Therefore, the data presented in this example strongly demonstrates that the conclusion made by the Office, *i.e.,* that the claimed invention has no real world use, is unsupportable. (*See also*, Watson Decla. ¶22(a)(2)(b)).

Receptor Function: Regulation of Cell Growth

Utilizing a northern blot analysis technique, a routine protocol, together with commercially available procedures, kits and reagents, three orphan GPCRs have been demonstrated to be up-regulated in tumor cell and cell lines. (*See*, Northern Blot Analysis Protocol, **Appendix D1**.

The results of RNA blots evidence that the orphan receptor 19Y was abundantly expressed in tumor uterus tissue ("T") when compared to the normal uterus ("N") cells, where no expression of 19Y was detected. (*See*, **Appendix D2**). Utilizing routine techniques, these data indicate that 19Y plays a role in the regulation of uterine carcinogenesis. Results of RNA blots for a second orphan GPCR, 18A, evidence that the 18A receptor is overexpressed in ovarian tumor tissue when compared to normal ovarian tissue. (*See*, **Appendix D3**, panel 1). In addition, expression of 18A was also detected in the tumor cells of three breast tissues as compared to normal breast tissues. (*See*, **Appendix D3**, panel 2). Again, utilizing the routinely applied technique of northern analysis, and assessing the expression pattern of 18A, the function of 18A was deduced, *i.e.,* 18A plays a role in regulating the proliferation of cells in the ovaries and breasts. The third orphan GPCR is referred to as 18AI. The RNA blots for the 18AI receptor evidenced an abundant expression in colorectal cancer cell lines (*e.g.,* SW480), indicating that 18AI plays a role in the colorectal carcinogenesis. (*See*, **Appendix D4**).

In these three examples, utilizing routine research techniques and skills well within the realm of scientists in this area, the expression patterns indicate that the receptors (*i.e.*, the mRNA) are up regulated in tumor cancer cells, and this associates the receptors with their respective pathological conditions, all in the absence of ***any*** discernable understanding of the corresponding endogenous ligands for these receptors. This substantial up-regulation is an apparent response to a defined condition, such as tumorgenesis. Accordingly, these examples point toward a function for an orphan receptor which can be determined without knowing the endogenous ligand, because of the differential expression patterns in normal tissue versus abnormal or diseased tissue. (*See*, Watson Decla. ¶22(a)(2)(c)).

After evaluating and selecting 19Y as a receptor target of interest for the regulation of tumorgenesis, the claimed invention was used with 19Y to directly identify two candidate compounds, Cmpd 1 and Cmpd 2. With the knowledge that 19Y is abundantly expressed in tumor cells, a routine proliferation assay technique was used (Roche Molecular Biochemicals, Cat. No. 1644807) as a method for quantifying cell proliferation. (*See*, Proliferation Assay Protocol, **Appendix D5**). In this assay, 19Y was transfected into prostate cancer cells (PC-3) and was measured in the presence and absence of the candidate compounds. (*See*, **Appendix D6**). According to the data of **Appendix D6**, 19Y, in the absence of any compound, evidence an induction of PC-3 cell proliferation when compared to the control ("CMV"). (*See*, red bar of Appendix D6). With the addition of the candidate compound, a decrease in cell growth was observed, as measured by the decrease in optical density when compared to the 19Y in the absence of compound. Thus, according to the definition of an inverses agonist, *i.e.*, a compound that inhibits the functional activity of a receptor, Cmpd 1 and Cmpd 2 are considered to be inverse agonists against the 19Y receptor. (*See,* yellow and blue bars of Appendix D6). These compounds, then, provide the ability to develop unique therapeutic candidates for the potential treatment of, *e.g.,* uterine cancer.

Utilizing routine skill and commercially available reagents and kits, 19Y was determined to be abundantly expressed in tumor cells of the uterus but not in the normal cells. Upon application of the claimed invention, two candidate compounds were identified and determined to inhibit the proliferation of prostate cancer cells. Stated again, based upon the expression pattern of 19Y, this receptor was determined to play a significant role in cancerous conditions. For that reason, the claimed method has allowed for the advancement

of a unique approach to the understanding and possible treatment of uterine cancer. Based upon the examples presented in this section, the claimed method provides for an irrefutable real world use of the claimed invention. (*See*, Watson Decla. ¶22(a)(2)(c)).

Receptor Function: Regulation of Ischemic Damage

Another commercially available technique for assessing receptor function was accomplished by utilizing data collected from homology analysis. This routine procedure was utilized with respect to an orphan GPCR 19BX by initially conducting a BLAST™ search, whereby the receptor protein of interest is used as a query in search for other similar or homologous sequences provided in the publicly available database, GenBank. Upon such a search, 19BX was determined to be homologous to a chemoattractant receptor, referred to as complement 5a receptor (C5a-R). Utilizing commercially available software, DNA STAR™, 19BX was determined to be about 30% homologous to C5a-R. (*See*, **Appendix E1**). C5a-R is a chemoattractant receptor that has been reported to be involved in inflammation.

In further evaluating 19BX as a receptor target of interest, a commercially available dot-blot kit (Clontech) was utilized to determine the receptor's expression pattern. The dot-blot evidenced that 19BX is expressed mainly in the brain, as indicated in columns 1 and 2 of **Appendix E2**. **Appendix E3** is a grid indicating the various tissues and their respective locations. Because 19BX receptor was specifically expressed in the brain, an in situ hybridization technique was utilized to evaluate 19BX in the brain. (*See*, In situ Hybridization Assay Protocol, **Appendix E4**). As outlined in **Appendix E5**, the arteries found in the brain of the rat were momentarily closed for one (1) hour, causing blood-flow to stop, thus leading to a buildup of blood pressure, also known as MCA occlusion. The arteries were then restored of their blood flow for various amounts of time, also referred to as reperfusion, and then analyzed for an up-regulation of 19BX. According to **Appendix E5**, an abundant expression of 19BX was evidenced specifically in the ipsilateral cingulated cortex, in a time dependent manner. (*See,* panels 1-9 of **Appendix E5**). In northern blot assay, 19BX was determined to be expressed on the neurons of the hippocampus. (*See*, **Appendix E6**).

In an effort to delineate the G protein coupling of 19BX, routine skills were utilized together with commercially available kits to determine that 19BX is a Gq linked receptor.

(*See*, AP1-Luc Reporter Assay Protocol, **Appendix E7**). **Appendix E8** indicates that both endogenous 19BX ("19BX wt") and a non-endogenous, constitutively activated version of 19BX couples to the Gq protein as evidenced in the increased luciferase signal when compared with the control ("CMV"). A receptor that couples to the Gq protein is mediated by calcium [Ca^{2+}]. The fact that 19BX signals via the Gq protein is indicative of readily understanding a protein (Gq) modulated by a constitutively activated orphan receptor (19BX). But this knowledge provides substantially more insight into the functional role of 19BX.

To summarize the functional role of 19BX, based upon the data presented herewith, it has been determined that when the brain is shocked or suffers from physical pain (*e.g.*, via MCA occlusion), 19BX is up-regulated. This up-regulation stimulates the coupling of Gq to 19BX, which then causes an influx of calcium into the cells. A surplus of calcium in the cell will eventually lead to the death of the cell. Therefore, based upon the data which evidence that: 19BX is up-regulated in response to an ischemic condition; 19BX is expressed in the brain, specifically in the neurons of the hippocampus; 19BX is Gq coupled, it was readily, a deduction to which Dr. Watson has agreed, that the functional role of receptor is involved in neuronal survival. (*See*, Watson Decla. ¶22(a)(2)(d)).

Receptor Function: Regulation of Injured Nerve Cells

Utilizing routine techniques and skill together with commercially available procedures, kits and reagents, orphan receptor 19M was determined to be expressed in Schwann cells. (*See,* Northern Analysis Protocol, **Appendix F1**). **Appendix F2** is a northern blot indicating that addition of forskolin at 20μM evidences that myelination was maintained. Schwann cell are significant in the sense that they act to repair injured nerves (also referred to as axons) by forming myelin sheaths around them. The greater the amount of myelin sheaths around the axons, the faster action potentials travel, thus allowing one's body to conserve more metabolic energy.

In another northern analysis assay according to that disclosed in **Appendix F1**, 19M was determined to be over-expressed in crushed rat sciatic nerves, specifically seven (7) days after crushing the nerves. (*See*, **Appendix F3**). Such data is consistent with the data presented in **Appendix F2**, *i.e.,* 19M evidences a role in the regeneration of nerves by stimulating the process of myelination in Schwann cells.

By utilizing routine skill and commercially available products, a functional role for 19M was deduced even without knowing the endogenous ligand. Upon selection of this receptor, followed by application of the claimed invention, an inverse agonist against 19M is preferred in diseases or disorders that are involved in hyper-myelination (*e.g.*, tumorgenesis), while an agonist is preferred in disease or disorders involved in hypo-myelination (*e.g.*, diabetes). (*See*, Watson Decla. ¶22(a)(2)(e)).

Summary of Response to Office Position 1

The functional role of an orphan receptor can be assessed and understood prior to identifying a receptor's endogenous ligand. As opined by Dr. Watson: where a receptor is expressed; the systems and circuits within which a receptor is located; how the receptor is expressed in normal versus disease state; and changes in receptor expression in response to certain conditions all provide the type of information that can readily guide the skilled artisan to deduce the functional role of a receptor. Simply stated, drug discovery does not require the identification of a receptor's endogenous ligand. Today, established pharmaceutical organizations such as Eli Lilly and Glaxo Wellcome recognize the need for faster and more cost-effective methods of finding modulators of receptors without having to spend several years and millions of dollars in search for the endogenous ligand.

Although knowing the endogenous ligand may be useful in understanding receptor function, as has been established herein, access to the endogenous ligand is not required to understand receptor function. The assignee of the application has provided numerous examples whereby the functional role of a receptor has been deduced by utilizing routine skill and techniques together with commercially available procedures, kits and reagents. Applicants respectfully note that these techniques are performed prior to applying the claimed invention as a means of assisting one skilled in the art to select a receptor target of interest. Selection of an orphan receptor is just that -- a matter of selection. Such selection is within the discretion of the artisan.

The claimed invention provides a real world use for the disclosed constitutively activated orphan receptors. Utilizing routine techniques, one skilled in the art is able to assess and understand the functional role of a receptor. Upon determining the role, the claimed invention can be applied to the disease/disorder/function. This is a real world use for the claimed invention. That the skilled artisan may decide to conduct additional studies

using such compounds (*e.g.,* medicinal chemistry to ascertain if more potent, cost-effective drugs can be developed) is not dispositive -- this is a function of ***all*** drug development. Rarely, if ever is a ***lead*** compound ***the*** drug that is marketed. A lead is just that -- a lead. This is a nuance of drug discovery; the Guidelines can make no judgment on this aspect of drug discovery because if this were the case, the Guidelines would prohibit securing a patent on anything other than those drugs proven to be safe and effective ***and*** approved for commercialization by the FDA.

In some embodiments, the receptors of the present invention can be used to identify inverse agonists and agonists, compounds that upon binding to the receptor target, modulate the function of a receptor compared to the receptor's natural functional activity. Stated differently, an inverse agonist of a constitutively activated receptor acts to shift the equilibrium of the receptor to an inactive state, thereby inhibiting the natural functional activity of the receptor. Conversely, an agonist of a constitutively activated receptor shifts the equilibrium of the receptor to the active state, thus activating the functional activity of the receptor. These two classes of compounds of a constitutively activated receptor can be directly identified because they impact the receptor's normal downstream signaling system. Because these downstream systems are based upon G proteins, one skilled in the art can understand the proteins modulated by an orphan GPCR. (*See,* Watson Decla. ¶18).

In addition to serving as lead drug candidates for drug discovery purposes, a significant and useful aspect of the claimed invention is that the discovery of inverse agonists and agonists provide for a better understanding of the cellular signaling response elements of a receptor. (*See*, Waston Decla. ¶18).

Based upon the data presented, Dr. Watson declares that the claimed invention provides for a well-established utility because, *e.g.,* drug discovery can be conducted with orphan GPCRs even when the endogenous ligand has not yet been identified. Further, in his opinion, the candidate compounds identified by the claimed method are within a class of compounds that, by definition, act to change the function of a receptor's endogenous functional activity. Thus, they do far more than merely "bind" to the receptor. In Dr. Watson's opinion, because GPCRs are coupled to G protein, any compounds identified will act to modulate these proteins, affecting the downstream functional activity of a receptor.

In view of the foregoing, Applicants submit that the basis of the rejection under 35 U.S.C. §101 predicated upon Position 1 cannot be sustained. Under a preponderance of

evidence, it is Applicants' position that they have more than met the burden shift. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn upon reconsideration.

Response to Office Position 2:

> "Similarly, constitutively activated orphan receptors have no known function."

G protein coupled receptors (GPCRs) are known to exist in equilibrium. GPCRs shift from an inactive state (R) to an active state (R*) and vice versa. The active state is typically stabilized by an endogenous ligand. This active state allows for the receptor to bind to its endogenous G protein where upon coupling of the G protein, several cascade of events may occur, *e.g.*, bound GDP is converted to GTP; and depending on which G protein couples to the receptor, adenylyl cyclase is stimulated or inhibited resulting in an increase or decrease, respectively, of cAMP; or an increase or decrease of inositol triphosphate.

In the mammalian body, constitutively activated receptors have been known in the art to play an important role in disease function. These naturally constitutively activated receptor versions shift the equilibrium to the activated state and remains in the active or "on" position without the need for the endogenous ligand, *i.e.*, GPCRs that are activated through a ligand-independent fashion are considered to be constitutively active receptors. These naturally active receptors may or may not be mutated, but have the same effect as a non-endogenous, constitutively activated GPCR, such that these receptors are stabilized in the "on" position, thereby causing the receptor to continuously stimulate the production of, for example, cAMP.

Naturally occurring constitutively active receptors, for example, thyrotropin receptor, lutenizing hormone receptor, rhodopsin receptor, V2 vasopressin receptor and adrenocorticortropic hormone receptor, have all been determined to consist of different versions containing deletions or alterations in the receptor sequence, which may cause receptor dysfunction. In these instances, the dysfunction can lead to an interference with the functioning of organs or systems that can be lethal, *i.e.,* gain of function or a loss of function. For example, a gain of function caused by a mutation in the GHRH receptor results in constitutive activation of the adenylyl cyclase. As the cAMP cascade is stimulated, growth hormone (GH) production is increased due to the overproduction of

cAMP, resulting in clonal hyperfunctional tumor. (*See*, Parma J. *et al.*, 100 *Mol Cell Endocrin*159 (1994)).

Table B below lists several naturally active receptors and the hereditary condition caused by the constitutively active receptor.

TABLE B

Receptor Name	Hereditary Condition
Thyrotropin receptor	Hyperthyroidism
Parathyroid hormone receptor	Parathyroidism
Lutenizing hormone receptor	Precocious puberty
Rhodopsin receptor	Retinitis pigmentosa
V2 vasopressin receptor	X-linked nephrogenic diabetes insipidus

The traditional approach to turning "off" a receptor is to search for an antagonist that would compete for the endogenous ligand. However, because constitutively active receptors are agonist-independent, an antagonist would be a compound whose binding does not alter the position of the equilibrium between the active state and the inactive state because there is no agonist to compete with. (*See*, Watson Decla. ¶17). Inverse agonists are compounds that preferentially stabilize the inactive conformation of a GPCR. As a result, inverse agonists to GPCRs display a decrease in intrinsic ability of a receptor to activate the cellular G protein coupling, and thus decrease the functional activity of the receptor. (*See*, Watson Decla. ¶17).

As illustrated above, 19AJ is an example of an endogenous, constitutively active receptor. (*See*, Appendix B2). However, this receptor does not contain a deletion or mutation that causes a disease or dysfunction. Instead, 19AJ has been determined to be specifically expressed in the islets of the beta cells in the pancreas, where upon glucose stimulation, insulin is secreted. Another example of an endogenous, constitutively active receptor is 18F, as illustrated above. (*See*, Appendix C2). Based upon the up-regulation of 18F in the hypothalamus, 18F was deduced to be involved in feeding behavior and upon direct identification of an inverse agonist to 18F, and subsequent in vivo evaluation, this deduction was confirmed. Similar to 19AJ, 18F receptor does not contain mutations or deletions, but is endogenously, constitutively active.

According to the numerous examples of the endogenous, constitutively active receptors, listed and discussed above, Applicants respectfully disagree with Position B

taken by the Office. It has been shown that several constitutively active receptors, including altered and unaltered receptors are found in the human body. Further, it has been reported that these constitutively active receptors that are naturally altered or mutated are capable of causing diseases. The mere existence of naturally active receptors in the body indicates that 19AJ and 18F are biologically functionally active. (*See,* Waston Decla. ¶22(b)(1)).

Applicants respectfully submit that these two examples, and other constitutively active receptors, have a biological functional purpose that is of substantial use; otherwise such receptors would not exist in the body. Therefore, because endogenous, constitutively active receptors have a substantial utility, the claimed method also must have a substantial utility -- it is the constitutively activated receptors that are utilized to identify candidate compounds that bind to the receptors.

Indeed, in Dr. Watson's opinion, it is both scientifically and factually incorrect to assert that constitutively activated orphan receptors have no known function. (*See,* Waston Decla.¶22(b)(1)). Again, in the absence of ***evidence*** to the contrary, the opinion alone requires a withdrawal of the rejection upon reconsideration.

In view of the foregoing, Applicants submit that the basis of the rejection under 35 U.S.C. §101 predicated upon Position B cannot be sustained. Accordingly, Applicants respectfully request that the rejection under Section 101 be withdrawn upon reconsideration.

According to the revised Utility Guidelines, and the reasonings and arguments submitted herewith, Applicants have clearly met their burden of providing evidence to establish that the claimed invention provides a specific *and* substantial utility. In addition, Applicants have proffered evidence in the Specification and in this Response that proves an immediately apparent well-established utility. Therefore, the view of *Oetiker* and the points cogently expressed by Deputy Assistant Commissioner Kunin, Applicants respectfully submit that the rejection under 35 U.S.C. §101 must be withdrawn upon reconsideration.

Brenner v. Manson Supports Applicant's Position that a "Real-World" Use has been Provided

The Utility Examination Guidelines and the Office Action both rely on *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) as a basis for explaining the concept behind the phrase "real world" use for a claimed invention to comport with 35 U.S.C.

§101. As with the Guidelines, the Office makes reference to the view asserted by the Supreme Court in *Manson*:

> Congress intended that no patent be granted on a chemical compound whose "utility" consists of its potential role as an object of use testing[.] [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

This well-settled, and oft-quoted, proposition is not disputed by Applicants. However, this quote, as used by the Office to support its conclusion of no "real world" use of the claimed invention, requires context. In a properly construed context, Applicants assert that *Manson* supports Applicants' position.

With due respect, the citation to *Manson* highlights the problems that can arise when a statement by a court is thrust naked into a legal discussion, without the benefit of the facts of the case which provide the required context.

Manson was taken upon writ of certiorari from a CCPA decision that reversed a Board of Appeals decision holding that Manson had established utility under 35 U.S.C. §101 for a claimed chemical process. Manson had attempted to provoke an interference proceeding with claims of a 1959 patent (U.S. Patent 2,908,693; attached hereto as **Appendix G**) having a claimed priority date of December 17, 1956. Manson, whose application was filed in January 1960, claimed that he had invented the process of the '693 patent prior to December 17, 1956.

The '693 patent issued with four process claims for production of 2-methyl-dihydrotesterones. Six examples were provided therein, all being directed towards production of such products. A single statement regarding the use of such products was provided in the specification:

> The products of the process of the present invention have a useful high anabolic-andriogenic ratio and are especially valuable for the treatment of those ailments where an anabolic or antiestrogenic effect together with a lesser androgenic effect is desired. Col. 1, lines 21-26.

Manson's application claimed the same process as the '693 patent. However, and proving to be a crucial fact, Manson disclosed ***no*** utility for the compound made by the process. Indeed, upon original rejection of the claims by the examiner under 35 U.S.C. §101, Manson attempted to support utility by reliance upon a 1956 article. The article

did not focus on the compound disclosed by Manson in his application; as noted by the *Manson* Court, the article cited by Manson:

> revealed the steroids of a ***class*** which ***includes the compound*** in question were undergoing screening for ***possible*** tumor-inhibiting effects in mice, and that a ***homologue*** adjacent to Manson's steroid had proven effective in that role. Emphasis supplied. 148 USPQ 690.

Manson provided absolutely no indication of any utility for the product made by the claimed process and, indeed, even his cited reference did not focus on the compound made by the Manson process, but rather a class that included the compound that, according to the reference, may prove to be useful in the role recited in the reference. Thus, without any utility for the compound provided by Manson in his original application, the Court agreed with the decision of the Board, and reversed the holding of the CCPA.

On these facts, the statements made by the Supreme Court are clear, and indeed, the Guidelines, *when properly applied*, would presumably lead to the same result reached by the original examiner who reviewed Manson's application, *i.e.*, with absolutely no disclosure of any utility for a product made by a claimed process, there can be no utility for that process under 35 U.S.C. §101.

However, when the Supreme Court's often cited quote is taken out of context, it is not difficult to understand that ***Manson*** is often used inappropriately. But ***Manson*** merely underscores the original Congressional intent behind the 1952 Patent Act regarding 35 U.S.C. §101 – an applicant must disclose some identifiable benefit for the claimed invention in order to be patentable under 35 U.S.C. §101.

A recent decision from the Court of Appeals for the Federal Circuit is helpful in this context. In *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (attached hereto as **Appendix I**), the claimed invention was directed to a "post-mix" beverage dispenser. Unlike a "pre-mix" dispenser that mixes the ingredients of a beverage prior to dispersion for customers, the claimed post-mix dispenser separates the ingredients which are not mixed until the beverage is dispensed; however, and simply ***for marketing purposes***, which purposes proved to be the lynch-pin for the asserted utility, the claimed post-mix dispenser was designed to look like a pre-mix dispenser, *i.e.*, a visible reservoir contained a fluid that looked like the beverage, and the reservoir looked

like the source of the beverage being dispensed to customers, even though it was not.

In an action for infringement, summary judgment was granted in favor of the alleged infringer, based on the conclusion that the claimed invention lacked utility and was therefore unpatentable under 35 U.S.C. §101. The Federal Circuit reversed, relying on *Manson* for support. As noted by the Federal Circuit and discussed above:

> The threshold of utility **is not high**: An invention is useful under Section 101 if it is capable of providing **some identifiable benefit**. Emphasis supplied. 51 USPQ2d at 1702.

Given that the Federal Circuit specifically relied upon the *Manson* decision for support, these three words are dispositive to issues under 35 U.S.C. §101: ***Some. Identifiable. Benefit.***

In essence, a long line of well-grounded case law has established that under 35 U.S.C. §101, the disclosure must merely provide an indication of usefulness of the invention – indeed, the threshold is so low under 35 U.S.C. §101 that it is ***only*** when a claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end that a rejection can properly be applied, and sustained, under 35 U.S.C. §101.

Applicants point out that as noted by the Supreme Court in *Manson*:

> A patent system must be related to the world of commerce rather than the realm of philosophy. 148 USPQ at 696.

When one thinks of "philosophical" discoveries that would fail under 35 U.S.C. §101, these are generally related to abstract ideas, such as a perpetual motion machine and "throw away" utilities (*e.g.,* a transgenic animal serving as snake-food), or theories, such as $E=MC^2$. It is simply unacceptable to assume that because a forward thinking inventor defines an invention that does not readily lend itself to the confines of a set of guidelines, that suddenly, with government-sponsored "magic", an invention that pre-Guidelines fully conformed with 35 U.S.C. §101, is somehow suspect post-Guidelines. There is nothing "philosophical" about the present invention.

Arena is a company that is founded on this technology. In April of 2000, Arena announced a drug discovery alliance with Eli Lilly & Company, one of the world's leading pharmaceutical companies. Dr. August M. Watanable, Executive Vice President, Science and Technology, for Eli Lilly, stated in a press release issued in connection with the

announcement of the collaboration that in reference to the technology covered by the claims pending in the application: "Arena has developed a very powerful platform for drug discovery that could substantially speed up the overall process for drug development." Watanabe, A.M., M.D., Eli Lilly News Press Release, April 17, 2000, attached hereto as **Appendix A**. During this collaboration, both Arena and Eli Lilly will select a number of GPCRs for activation utilizing the claimed method. This collaboration is on-going.

On May 29, 2000 Arena entered into a collaboration with Taisho Pharmaceutical Co., Ltd. This collaboration involves application of the technology covered by the pending claims to orphan GPCRs of interest to Taisho. This collaboration is also on-going.

Clearly, these collaborations provide further proof of the "real-world" value of the claimed invention. Major pharmaceutical corporations do not invest in collaborations dealing with the "realm of philosophy". Clearly, these collaborations involving the claimed subject matter involve the "world of commerce".

In the present application, Applicants have, ***at a minimum***, fully disclosed ***some identifiable benefit*** for the claimed invention. Even under Section 112, which has a higher level of utility than 35 U.S.C. §101, an Applicant is not required to provide examples or evidence of all matters covered by a genus claim, so long as sufficient disclosure, coupled with ordinary skill, is provided as to how to make and use the claimed invention. Indeed, Applicants have provided examples of the use of the claimed invention by providing data that exemplifies the steps set forth in the claims.

Summary of Utility Arguments and Proofs

Under 35 U.S.C. §101, the utility threshold is not high.

Applicants have identified a problem that has plagued many institutions since the explosion of readily available and easily usable genetic tools which have made accessible a plethora of receptor targets – how to exploit these targets for the betterment of the human condition. Applicants have disclosed, and the Watson Declaration makes clear, that the location and expression of a receptor are quite readily capable of determination and are useful tools to define insight into receptor function. Applicants have not focused on, nor do they claim, such function ***nor*** do they claim all orphan receptors. Rather, Applicants have discovered that by ignoring the art-directed focus on endogenous ligand discovery, and instead boldly moving in a unique direction towards constitutively active

orphan receptors, one can, using, *e.g.,* the tools disclosed by Applicants, directly identify two functionally-defined types of compounds that can be directly identified using the constitutively active receptor: an inverse agonist or an agonist. These types of compounds have a recognized and well-defined meaning in the art (in addition to being defined in the specification) that are predicated upon a functional receptor response, and not mere receptor-binding. The mere selection of a receptor is based upon the needs of the artisan who reviews the application and uses her routine skill -- but once that selection has been made, Applicants' disclosure and teaching as to how to avoid the need for using an endogenous ligand for direct identification of a functional modulator of the receptor, *i.e.*, an inverse agonist or agonist, is quite valuable – and here, too, it is then a matter of mere selection by the artisan to determine if the needs of that artisan require an inverse agonist to reduce receptor function, or an agonist to enhance receptor function, these decisions being based upon the artisan's selection of a particular receptor of interest.

Applicants assert that they have not requested a mere "hunting license." Indeed, under both *Manson* and *Orange Bang*, the claimed invention has more than met the low threshold of Section 101 of providing ***some identifiable benefit***.

The Office simply cannot, in good faith, maintain the position that under these facts, with these data, and with this disclosure, that the claimed invention is totally incapable of achieving any useful result or incapable of serving any beneficial end.

Applicants have set forth evidence that the claimed subject matter has a specific utility. Accordingly the claimed invention complies with the requirements for patentability as existed before the promulgation of the Utility Examination Guidelines. As noted above, the PTO has declared that "***The Guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112".*** Accordingly, the claimed invention must comply with the requirements for utility as described in the Utility Examination Guidelines unless the Patent Office has changed the law.

As discussed above, the Office has acknowledged that "an orphan receptor when directly correlated to a known function, such as affecting food intake or a disease state would have a utility in a method for directly identifying its agonist." (Office Action at page 4). Applicants have previously submitted such correlations. Nothing more than routine laboratory experimentation would be required to determine the localization of a

given receptor and thereby the correlated physiological function.

Notwithstanding the foregoing, as discussed above, Applicants have provided evidence that the claimed invention possesses a specific and substantial utility, therefore complying with the utility requirement as exists under the Utility Examination Guidelines.

Applicants reiterate that based upon Dr. Watson's extensive and well documented scientific background and the esteemed scientific reputation that he has established over the past twenty years, his opinions ***must*** carry great weight, and in the absence of ***evidence*** to rebut Dr. Watson's opinions, or in the absence of an Examiner's opinion to the contrary, the rejections must be withdrawn. The Guidelines have served their intended purpose in this case by allowing the Office to provoke judicious evidence from Applicants, but they cannot be maintained as a basis for a rejection under 35 U.S.C. §101.

Applicants respectfully request the withdrawal and reconsideration of the rejections under 35 U.S.C. §101. The pending claims satisfy the requirements of 35 U.S.C. §101.

Claims Rejected Under 35 U.S.C. §112, First Paragraph

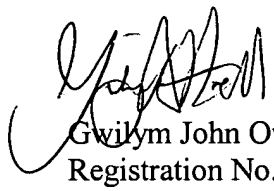
Claims 33, 34, 39-40, and 45-68 were rejected under 35 U.S.C. §112, first paragraph because "one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention."

Claims 33, 34, 39-40, and 45-68 were rejected under 35 U.S.C. §112, first paragraph solely because the claimed invention allegedly did not provide for a well-established utility nor a substantial utility. Because Applicants have established a well-established utility and a substantial utility that would constitute a real world use, one skilled in the art would clearly know how to use the claimed invention. Therefore, Applicants respectfully request that this rejection also be withdrawn upon reconsideration.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The foregoing represents a *bona fide* attempt to advance the present application to allowance. Applicants respectfully invite the Examiner to contact the undersigned at (215) 564-8338 to discuss any issues unresolved by this response. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



Gwilym John Owen Attwell
Registration No. 45,449

Date: April 10, 2002
WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

Attachments:

"Version with markings to show changes made"
Copy of Declaration of Stanley J. Watson, M.D., Ph.D. and Attachments thereto

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please amend claims **34, 40, 45, 52, 53, 60 and 63-68** as follows:

Claim 34 **(Amended)** The method of claim [33] 69 wherein the compound is determined to be an inverse agonist to said receptor.

Claim 40 **(Amended)** The method of claim [39] 70 wherein the compound is determined to be an inverse agonist to said receptor.

Claim 45 **(Amended)** The method of claim [33] 69 wherein the third intracellular loop of the receptor of step [(b)] (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

Claim 52 **(Amended)** The method of claim [33] 69 wherein the second intracellular loop of the receptor of step (b) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

Claim 53 **(Amended)** The method of claim [39] 70 wherein the third intracellular loop of the receptor of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

Claim 60 **(Amended)** The method of claim [39] 70 wherein the second intracellular loop of the receptor of step (a) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

Claim 63 **(Amended)** The method of claim [33] 69 wherein said mammal of step [(h)] (d) is a human.

Claim 64 **(Amended)** The method of claim [39] 70 wherein said mammal of step [(i)] (d) is a human.

Claim 65 **(Amended)** The method of claim [33] 69 wherein said mammal of step [(h)] (d) is a non-human.

Claim 66 **(Amended)** The method of claim [39] 70 wherein said mammal of step [(i)] (d) is a non-human.

Claim 67 **(Amended)** The method of claim [33] 69 wherein said physiological function [of step (b)] is an abnormal physiological function.

Claim 68 **(Amended)** The method of claim [39] 70 wherein said physiological function [of step (c)] is an abnormal physiological function.

Please cancel claims **33** and **39** without prejudice.

Please add new claims **69-76,** as follows.

Claim 69 **(New)** A method for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous G protein coupled receptor (GPCR), wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising the steps of:

(a) subjecting said GPCR to constitutive receptor activation to create a constitutively activated GPCR;

(b) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(c) identifying said non-endogenous candidate compound as an inverse agonist or an agonist to said constitutively activated GPCR by measuring at least a 30% difference in a reporter signal induced by said contacted compound as compared with a reporter signal in the absence of said contacted compound.

Claim 70 **(New)** A method for directly identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous constitutively activated G protein coupled receptor (GPCR), wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising the steps of:

(a) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(b) identifying said non-endogenous candidate compound as an inverse agonist or an agonist to said constitutively activated GPCR by measuring at least a 30% difference in a reporter signal induced by said contacted compound as compared with a reporter signal in the absence of said contacted compound.

Claim 71 **(New)** A compound directly identified by the method of claim 69.

Claim 72 **(New)** A compound directly identified by the method of claim 70.

Claim 73 **(New)** A pharmaceutical composition comprising the compound of claim 71.

Claim 74 **(New)** A pharmaceutical composition comprising the compound of claim 72.

Claim 75 **(New)** The method of any one of claims 69 or 70 wherein said location of expression of said receptor and said correlated physiological function are selected from

the group of locations and correlated physiological functions consisting of groups 1-147 as follows:

1. gastrointestinal tract smooth muscle / motility of stomach and intestines;
2. gastrointestinal tract ganglionic nerve fibers / motility of stomach and intestines;
3. urinary tract smooth muscle / ureter function and urinary bladder function;
4. salivary gland / salivary secretion;
5. alpha cells of the pancreas / secretion of glucagons;
6. beta cells of the pancreas / secretion of insulin;
7. uterine smooth muscle / uterine contraction;
8. heart muscle / contractility of heart muscle;
9. vascular smooth muscle / contractility of smooth muscle;
10. adipocytes / lipolysis;
11. platelets / platelet aggregation in response to blood vessel injury;
12. skeletal neuromuscular junction / skeletal muscle contractility;
13. bronchial smooth muscle / respiration;
14. nasal mucosal blood vessels / mucosa volume;
15. trigone muscle of bladder and urethra / urinary outflow;
16. chondrocytes / cartilage formation;
17. ciliary body of the eye / aqueous humor production;
18. thyroid / thyroid hormone secretion;
19. mast cells / immediate hypersensitivity reactions;
20. basophils / immediate hypersensitivity reactions;
21. osteoblasts / bone remodeling;
22. osteoclasts / bone remodeling;
23. brain capillary endothelial cells / permeability of blood-brain barrier;
24. T cells / immune response;
25. B cells / immune response;
26. kidney proximal tubular epithelial cells / organic acids exchange;
27. neutrophils / immune response;
28. eosinophils / immune response;
29. monocytes / immune response;
30. kidney late distal tubule / organic bases exchange;

31. collecting duct principal cells / organic bases exchange;

32. kidney granular juxtaglomerular cells / secretion of rennin;

33. peripheral postganglionic adrenergic neurons / sympathetic function;

34. hepatocytes / synthesis of cholesterol and lipoprotein;

35. gastrointestinal parietal cells / secretion of stomach acid;

36. gastrointestinal superficial epithelial cells / secretion of cytoprotective factors, mucus and bicarbonate;

37. epidermal cells / skin maintenance;

38. bone marrow stem cells / erythropoesis production;

39. angle structures of the eye / aqueous humor outflow;

40. uveoscleral structures of eye / aqueous humor outflow;

41. suprachiasmatic nucleus / circadian rhythm;

42. baroreceptors / blood pressure;

43. basal ganglia / movement control;

44. periaqueductal grey and dorsal horn of spinal cord / nociception;

45. area postrema / vomiting;

46. thalamus / sensorimotor processing and arousal;

47. sensorimotor cerebral cortex / sensorimotor processing;

48. spinal cord motor neurons / motor function control;

49. dorsal root ganglion neurons / sensory information transmission;

50. oligodendrocytes / neuron myelin sheath production;

51. nucleus basalis / cognition and memory;

52. nucleus accumbens / addictive cravings;

53. lateral reticular formation of medulla / vomiting;

54. hypothalamic neurons containing growth hormone releasing factor (GHRH) / secretion of GHRH;

55. hypothalamic neurons containing somatostatin / secretion of somatostatin;

56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH) / secretion of TRH;

57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH) / secretion of GnRH;

58. hypothalamic neurons containing corticotropin releasing factor (CRF) / secretion of CRF;
59. anterior pituitary somatotropes / secretion of growth hormone;
60. anterior pituitary lactotropes / secretion of prolactin;
61. anterior pituitary gonadotropes / secretion of luteinizing hormone;
62. anterior pituitary gonadotropes / secretion of follicle stimulating hormone;
63. anterior pituitary corticotropes / secretion of adrenocorticotropic hormone;
64. leydig cells of the testes / secretion of testosterone;
65. sertoli cells of the testes / spermatogenesis;
66. granulosa cells of the ovary / synthesis of estrogen;
67. theca cells of the ovary / synthesis of estrogen;
68. synovium / joint function;
69. amygdala / modulation of emotion;
70. pineal gland / regulation of circadian rhythm;
71. nucleus of the solitary tract / cardiovascular regulation;
72. caudal ventrolateral medulla / cardiovascular regulation;
73. rostral ventrolateral medulla / vasopressor activity;
74. parabrachial nucleus / taste aversion response and nociceptive response;
75. entorhinal cortex / cognition;
76. pyriform cortex / cognition;
77. temporal cortex / memory acquisition;
78. frontal cortex / regulation of emotional response and memory acquisition;
79. parietal cortex / visual acuity, touch perception, and voluntary movement;
80. occipital cortex / visual acuity;
81. hippocampus / learning and memory;
82. dentate gyrus / learning and memory;
83. midbrain reticular formation / arousal;
84. supraoptic nucleus of the hypothalamus / reproductive functions;
85. magnocellular of the hypothalamus / modulation of stress, blood pressure and lactation;
86. parvocellular neurons of the hypothalamus / metabolism;
87. arcuate nucleus of the hypothalamus / release of pituitary hormones;

88. trigeminal area / cerebral vessel dilation and blood pressure;

89. cerebral blood vessels / cerebral vessel dilation;

90. brain stem / breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature;

91. ventral lamina terminalis / blood pressure;

92. vagus nerve / blood pressure and heart rate;

93. nucleus of the solitary tract / blood pressure;

94. adrenal medulla / catecholamine response to stress;

95. adrenal cortex / stress-induced corticosterone release;

96. locus coeruleus / arousal and response to stress;

97. substantia nigra / control of body movement;

98. ventral tegmental area / control of body movement;

99. olfactory bulb / odor perception;

100. median eminence of hypothalamus / pituitary function;

101. raphe nuclei / sleep and arousal;

102. habenula / sexual activity;

103. cerebellum / control of body movement;

104. posterior hypothalamus / intestinal motility and blood pressure;

105. dorsal medulla / blood pressure;

106. lateral hypothalamus / food intake and stomach acid secretion;

107. rostral hypothalamus / heart rate;

108. pontine-medullary reticular formation / respiration and heart rate;

109. medulla / respiration and heart rate;

110. mesencephalon / heart rate;

111. ventral hypothalamus / response to stress;

112. paraventricular nucleus of hypothalamus / response to stress;

113. preoptic area of hypothalamus / sexual activity;

114. mammillary region / food intake;

115. perifornical area of hypothalamus / food intake;

116. ventromedial hypothalamus / food intake;

117. pons/reticular formation / arousal and wakefulness;

118. septum / emotional control;

119. pedunculopontine tegmental nucleus / arousal;
120. astrocytes / neuronal metabolism;
121. microglia / response to neuronal injury;
122. choroid plexus / production of cerebrospinal fluid;
123. Schwann cells / myelination of peripheral nerves;
124. endoneurium / production of connective tissue nerve sheath;
125. lateral spinothalamic pathway / response to pain and temperature stimuli;
126. ventral spinothalamic pathway / touch sensation;
127. dorsal column-medial lemniscal pathway / touch sensation;
128. free nerve endings / response to pain and temperature;
129. hair follicle endings / touch sensation;
130. Krause's end-bulb / temperature sensation;
131. Meissner's corpuscles / touch-pressure sensation;
132. Merkel's disk / touch-pressure sensation;
133. Pacinian corpuscle / touch-pressure sensation;
134. Ruffini's corpuscle / temperature sensation;
135. retina / visual acuity;
136. parathyroid gland / calcium balance;
137. placenta / placental activity;
138. skeletal muscle fibers / muscle contraction;
139. copora cavernosum / genital vasodilation;
140. corticospinal tract / movement control;
141. motor cerebral cortex / movement control;
142. postganglionic neurons / control of blood pressure and adrenal activity;
143. intramural ganglion / distal colon peristalsis;
144. hypogastric plexus / control of urethral and anal sphincters;
145. pelvic plexus / genital vasodilatation and penile erection;
146. vesical plexus / urinary bladder control; and
147. celiac plexus / intestinal peristolisis.